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Comparison of the etiology of stillbirth over five decades in a single centre: a retrospective study

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ABSTRACT

Comparison of the etiology of stillbirth over five decades in a single centre: a retrospective study

Objective: To compare the rates and etiologies of stillbirth over the past 50 years.

Study Design: We reviewed all autopsy reports for stillbirths occurring between 1989 and 2009 at the McGill University Health Centre to determine the etiology of stillbirths. We also reviewed maternal characteristics. We compared our results with a previous study published in 1992 on etiologies of stillbirth from 1961-1988 at the same institution.

Results: Amongst 79,410 births from 1989-2009, 217 stillbirths were included in our study. The mean maternal age was 31,05 (± 5.8) years. In 28.1% of cases, there was a prior history of subfertility. The mean gestational age at diagnosis was 32.69 (± 5.58) weeks, with a birth weight of 1,888 (± 1,084) grams. The main causes of stillbirth were unexplained antepartum asphyxia (26.7%), placental factors (19.8%) and abruptio placenta (12.9%). Other causes included hematogenous or ascending infection (10.6%), fetal malformations (8.3%), maternal hypertension (3.2%), intrauterine growth restriction (2.8%), diabetes (1.8%) and intra-partum asphyxia (1.4%). Other fetal causes were found in 12.4% of cases.

Conclusions: Due to detailed pathological examination of most stillbirth cases over the last five decades at our tertiary obstetrical centre, we could study the trends in the etiology of stillbirths in a cohort of more than 150,000 births. In 50 years, the rate of stillbirth has decreased from 115 to 19.9 cases per 10,000 births, which represents a reduction of 83%. Antepartum asphyxia of unknown origin remains the most common contributor to stillbirth, with 40% of these cases occurring in late pregnancy.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. Despite the great numbers of papers recently published on stillbirths, we are one of the few institutions in North America who have been able to create a complete obstetrical and neonatal database with consistent pathological examination throughout the last five decades.

2. However, there are a few limitations to our paper. Given the fact that our institution is a tertiary referral centre, our specific patient populations, with a greater proportion of high-risk pregnancies, may not exactly represent the general patient population in most community hospitals. Our results may be somewhat influenced by this tertiary center bias.

3. Also, the study of each aetiology is somehow limited to a small number of cases per decade given the decreasing incidence of stillbirths with improved obstetrical care in the past decades.

4. Another limitation is from the fact that 72 of our stillbirths could not be included in the analysis of the trend of aetiologies due to incomplete pathology examination or autopsy refusal. This represents almost a quarter of the cases of stillbirths during the study period. However, as protocols for stillbirth are being developed as standard obstetrical care, the use of autopsy examination should be more prevalent.

INTRODUCTION

Stillbirth is defined as the death before birth of a fetus before the 20th week of gestation or h a weight less than 500g[1]. Worldwide, stillbirth remains the most prevalent adverse outcome of pregnancy, estimated at 2.64 million in 2009[2] and 1 in 160 pregnancies in the United States[3]. The rates of stillbirth remain highest in developing countries but likely underestimated due to the both poor access to obstetrical care and the limited recordkeeping[4]. Among the various recognized etiologies of stillbirth, obstetric complications and placental abnormalities remain the most common in developed countries[5]; however, a recent increase in the proportion of stillbirths caused by congenital malformations has been noted[6]. The rate of unexplained antepartum asphyxia has remained the same over the last decades[7-8]. Maternal obesity and advanced maternal age are now thought to contribute to an increasing proportion of stillbirths[9-10].

This study aims to examine and evaluate the rates and etiologies of stillbirths over the past 20 years at the McGill University Health Center (MUHC). A previous study at this institution evaluated the period from 1961-1988 and demonstrated that unexplained antepartum asphyxia was the major cause of death[11]. We will also compare our current data with the historical data previously derived.

MATERIAL AND METHODS

A retrospective cohort study was conducted at the McGill University Health Center (MUHC) with data from the Royal Victoria Hospital, a tertiary-care centre and one of the main referral centers in the province. At this institution it has for many decades been the standard practice for all patients with a stillbirth to be offered a complete fetal autopsy and for all placentas to routinely be examined by a specialised team of technicians and perinatal pathologists.

All autopsy reports of stillbirths delivered between 1989 and 2009 were retrieved from our pathology database. For this study, the definition of stillbirth was defined as the birth of a fetus weighing 500g or more with no signs of life. Pregnancy terminations were not included in this study. A detailed external and internal examination of the fetus with microscopic examination of fetal and placental tissues is performed following a standard protocol.

We recognise that more than one cause may have contributed to any individual fetal death. However, pathological examination with clinical correlation was used to determine the most likely primary cause. To facilitate comparison with the earlier cohorts examined within our institution, the primary causes of fetal death were classified according to similar guidelines as described in Table 1[11]. The cases that were not attributable to any of the principal categories were classified as "others" with these in turn being sub-divided as fetal or placental causes, depending on the final autopsy conclusions. All specific causes, comprising the "others" category, are also listed in Table 1.

Table 1. Classification of primary causes of fetal death	
Abruptio placentae	Fetal death associated with antepartum bleeding and retroplacental blood clot, excluding placenta previa
Maternal diabetes	Otherwise unexplained fetal death of appropriate for gestational age infants of diabetic or glucose-intolerant mothers
Infection	Fetal death in which the fetus and/or the placenta show evidence of infection on pathologic examination, with or without clinical signs of maternal infection
Intrapartum asphyxia	Asphyxia related to labor and delivery, death without placental, cord, fetal, or maternal cause. This group is subdivided into deaths related to dystocia labor or malpresentation, and those otherwise unexplained deaths occurring during apparently normal labor.
Fetal growth restriction	Asphyxia or otherwise unexplained fetal death in a fetus 25% underweight (2.4^{th} percentile) for gestational age at time of death.
Isoimmunization	Abnormal maternal antibodies and evidence of excessive fetal erythropoiesis
Malformation	Potentially lethal anomalies take precedence over all other conditions
Maternal Hypertension	Otherwise unexplained fetal death of appropriate for gestational age infants in hypertensive mothers
Unexplained antepartum asphyxia	Death of an appropriate for gestational age fetus before labor with no evident fetal, maternal, or placental abnormality (with or without cord loops/knots)
Others – Placental causes	Includes placental insufficiency, placental infarct, cord accident, cord thrombosis, cord prolapse, vasculopathy
Others – Fetal causes	Includes fetal blood loss, hydrops, twin-to-twin transfusion syndrome, fetal-maternal hemorrhage, fetal shock, fetal coagulopathy, decreased uteroplacental blood flow

We used the "Montreal Obstetrical and Neonatal Database" (MOND), which is a comprehensive computerised database of obstetrical and neonatal data for all pregnancies delivered at the MUHC, Montreal, Canada, to retrieve relevant maternal information that could have affected pregnancy outcomes. Accuracy of fetal characteristics including gestational age, birth weight and gender were also cross-referred between the pathology and the MOND database. Hypertension complicating pregnancy was defined as any hypertensive disorder diagnosed during pregnancy, whether chronic (prior to 20 weeks of gestation), pregnancy-induced hypertension or pre-eclampsia. Diabetes at the time of delivery included impaired glucose tolerance and all classes of

diabetes from A1 to T (White Classification)[12]. Subfertility was defined as at least one year of unprotected intercourse before the current pregnancy. Intrauterine growth restriction was defined as a birth weight less than the 5th percentile for gestational age following the United States National Reference for Fetal Growth[13]. Continuous variables were all described by mean values and standard deviations. Categorical variables were described by total numbers and percentages. Stillbirth rates were described per 10,000 live births as in the previous paper. Statistical analysis was performed with SPSS statistical software (PASW 20, IBM, Armonk, NY, USA). Odds ratios, 95% confidence intervals and differences between categorical variables were analysed using chi-square or Fisher's exact tests as appropriate. Differences between continuous variables were tested using independent sample t tests if normally distributed and otherwise by the Mann-Whitney U test. P values of <0.05 (two-sided) were considered to indicate statistical significance. Scientific review and ethical approval for this study were granted by the McGill University Health Centre's institutional review board.

RESULTS

From a cohort of 79,410 births that delivered at the Royal Victoria Hospital between 1989 and 2009, 332 pathology reports for stillborn fetuses were retrieved. Of those, 43 were identified as terminations of pregnancy for medical or fetal indications and were excluded. Of the remaining 289 stillbirths, 70 did not undergo complete autopsy examination, primarily due to parental refusal. The overall autopsy rate was therefore 76%. Two cases were rejected from the study because of possible interpretation bias. The first case was the death of a newborn, delivered at home and where death was declared at the hospital soon after birth. The second case was excluded because placental pathological examination had not been performed. The final study population consisted of 217 stillbirths, although overall rates for this period were calculated from the total 289 stillbirths.

Table 2. Baseline maternal and fetal characteristics of the 217 stillbirth cases

	Total cases N (%)	Average ± SD
Maternal age	--	31.05 ± 5.86
Gravida	--	2.48
Parity	--	0.80
Aborta	--	0.68
Multiple gestation	23 (10.6%)	--
Infertility	65 (30.0%)	--
Smoking	43 (19.8%)	--
Cannabis use	9 (4.2%)	--
Previous cesarean	21 (9.7%)	0,12
Cesarean birth	23 (10.6%)	--
Gestational hypertension	23 (10.6%)	--
Gestational diabetes	12 (5.5%)	--
Female fetuses	102 (47.0%)	--
Male fetuses	115 (53.0%)	--
Gestational age (weeks)	--	32.69 ± 5.58
Birth weight (gram)	--	1888 ± 1084

We first examined the maternal characteristics of these stillbirths (Table 2). The mean maternal age was 31.05 ± 5.86 years. The mean gravidity, parity and number of prior abortions were 2.48, 0.80 and 0.68 respectively. In our study population, 23 patients (10.6%) had a twin pregnancy; 43 (19.8%) were smokers; 23 (10.6%) had hypertension and 12 (5.5%) had diabetes. In 65 cases (30.0%), there was a prior history of subfertility. The mean gestational age at the stillbirth delivery was 32.69 ± 5.58 weeks, with a birth weight of 1888 ± 1084 grams. Of the 217 cases of stillbirth with full autopsy, 142 cases occurred in the decade from 1989 to 1999, and 75 cases occurred between 2000-2009, which is approximately a 50-percent reduction in the number of stillbirths from one decade to the next (Table 3). There are 52 stillbirth cases (24.0%) that occurred before 28 weeks gestation; 72 cases (33.1%) between 28 and 34 weeks; 79 cases (36.4%) between 34 and 40 weeks; and the remaining 14 cases (6.5%) after 40 weeks (Table 3). The rates of prematurity were proportionally similar between the two studied decades (24% before 28 weeks and 57% before 34 weeks). The rate of pregnancies exceeding 40 weeks also remained unchanged from 1989-1999 to 2000-2009.

TABLE 3. Fetal deaths by gestational age from 1989-2009

Gestational age (weeks)	1989–1999	2000–2009	TOTAL
< 28	34	18	52
28 - 34	47	25	72
34^{+1} - 40	51	28	79
> 40	10	4	14
TOTAL	**142**	**75**	**217**

The most common cause of stillbirth was unexplained antepartum asphyxia (n=58, 26.7%) (Table 4). Unexplained antepartum asphyxia as a cause of stillbirth decreased from 45 cases (31.7%) between 1989 and 1999 to only 13 cases (17.3%) in the subsequent decade. This

represents a near 50% reduction of the rate of unexplained antepartum asphyxia as a cause of fetal death from the previous decade. We also evaluated the unexplained fetal deaths by gestational age (Table 5). Nearly 40% (n=23) of these cases occurred in later pregnancy, between 34 and 40 weeks. There were only seven cases (12.1%) in the post-dates period, 12 cases (20.7%) in gestations < 28 weeks and 16 cases (27.6%) in gestations between 28 and 34 weeks.

TABLE 4. Causes of death among stillbirths from 1989-2009

CAUSE	1989–1999	2000–2009	TOTAL
Abruptio placenta	15	13	28
Maternal diabetes	4	0	4
Infection	19	4	23
Chorioamnionitis	*14*	*3*	
Cytomegalovirus	*0*	*1*	
Parvorirus B19	*3*	*0*	
Villitis	*2*	*0*	
Intrapartum asphyxia	2	1	3
Intrauterine growth restriction	6	0	6
Malformation	12	6	18
Maternal Hypertension	5	2	7
Unexplained antepartum asphyxia	45	13	58
Other – placental causes	18	25	43
Other – fetal causes	16	11	27
TOTAL	**142**	**75**	**217**

TABLE 5. Unexplained fetal deaths by gestational age from 1989-2009

Gestational age (weeks)	1989–1999	2000–2009	TOTAL
< 28	7	5	12
28 - 34	12	4	16
34^{+1} - 40	19	4	23
> 40	7	0	7
TOTAL	**45**	**13**	**58**

Abruptio placentae was the second most common cause, identified in 28 cases overall (12.9%) with a similar number of cases in both decades (15 and 13 cases respectively). Although this appears to represent a slight increase in the rate of stillbirth secondary to abruptio placenta from 10.6% to 17.3%, this difference is not statistically significant (p=0.116). Infection, including ascending and hematogeneous infections, was the primary factor in 23 cases (10.6%) with a marked decrease of cases in 2000-2009 compared to 1989-1999 (19 cases, 13.4% and 4 cases, 5.3% respectively), a difference that reached significance (p=0.05). Most infectious cases were from ascending chorioamnionitis with 14 cases (9.9%) occurring during 1989-1999 and only three cases (4.0%) during 2000-2009; the former decade including three cases of Parvovirus B19 and two of unspecified villitis and the latter including one case of Cytomegalovirus. Intrauterine growth restriction was identified as the primary etiological factor in six stillbirths (2.8%), none of which occurred in the later decade. Given the small number of cases this difference was not found to be statistically significant (p=0.076).

Other placental or umbilical cord factors accounted for 43 cases (19.8%); and their rate increased from 12.7% to 33.3% from 1989-1999 to 2000-2009. The majority of these were placental infarcts and cord accidents: 15 cases (21.4%) and 16 cases (22.9%), respectively. The other cases include placental insufficiency, cord prolapse, thrombosis and vasculopathy (Table 6). Fetal malformations accounted for 18 cases (8.3%) whilst other fetal causes, such as fetal blood loss, twin-to-twin transfusion syndrome, hydrops, feto-maternal haemorrhage, fetal shock and coagulopathy, accounted for 27 cases (12.4%). Although the overall rate for a fetal cause of the stillbirth remained stable, there were no cases of hydrops in the latter decade 2000-2009. The remaining cases were attributable to maternal hypertensive disorders (3.2%), diabetes (1.8%) or

intra-partum asphyxia (1.4%); the frequencies of these were essentially unchanged across the two decades except for diabetes which was not a primary factor in any cases in the period 2000-9 (Table 4). Of note, no stillbirth consequent to iso-immunization occurred during either of these two decades.

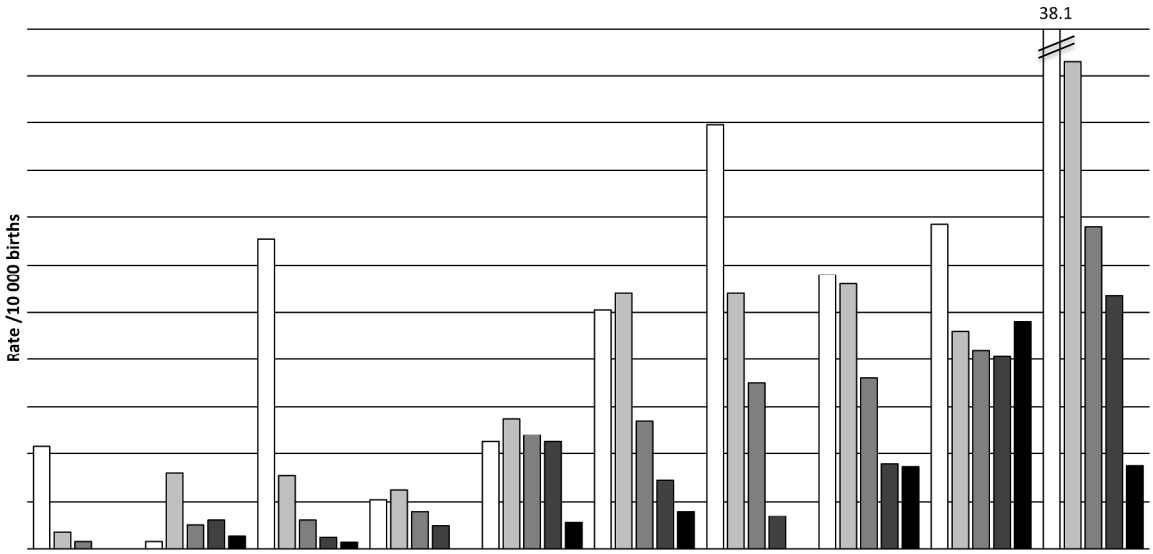
Table 6. Fetal deaths due to miscellaneous causes

	1989-1999	2000-2009	TOTAL
PLACENTAL CAUSES	**18**	**25**	**43**
Placental insufficiency	0	5	5
Placental infarct	7	8	15
Cord accident	9	7	16
Cord prolapse	0	1	1
Cord thrombosis	0	2	2
Vasculopathy	2	2	4
FETAL CAUSES	**16**	**11**	**27**
Fetal blood loss	2	2	4
Twin-to-twin transfusion	4	2	6
Hydrops	5	0	5
Fetal-maternal hemorrhage	4	3	7
Fetal shock	1	1	2
Fetal coagulopathy	0	2	2
Decreased uteroplacental blood flow	0	1	1

Our study results were compared with data from previous decades at this single institution. First of all, the total number of births per decade has increased significantly from 29,101 births in the 1960s to 37,537 births in the 2000s. There was a major overall improvement in the rates of stillbirths over the decades: 115 per 10,000 births in the 1960s, 51 per 10,000 births in the 1980s, 41 per 10,000 births in the 1990s and 32 per 10,000 births in the 2000s. The above rates took into account the 72 stillbirth cases excluded from the study due to incomplete pathological

examination. This represents a 73% reduction in the overall rate of stillbirths from 1960 to 2009. Specific aetiologies of the 217 examined stillbirths were also compared to the previous study at the same institution. Unexplained stillbirths decreased from 38.1 per 10,000 births in the 1960s to 20.6 in the 1970s, 13.6 in the 1980s and 7.3 in our current study. The numbers of stillbirths secondary to abruptio placentae was relatively stable in our study period: 3.6 per 10,000 births in the 1990s and 3.5 per 10,000 births in the 2000s. This was a significant reduction from previous decades: 11.6 per 10,000 in 1960s, 11.2 per 10,000 in 1970s and 7.2 in the 1980s. The rate of stillbirths due to infectious causes remained stable at 4.5 per 10,000 births over the decades until the most recent decades (2000s) where the rate dropped to 1.1 per 10,000 births. The rates of stillbirths from intra-partum asphyxia, malformations, diabetes and maternal hypertension have dramatically decreased over the decades (Figure 1). There are no cases of Rhesus iso-immunization compared to 4.3 per 10,000 births in the 1960s. It would be difficult to compare the rates of stillbirths from other causes, as these were not classified as placental or fetal causes in the previous study. However this category remained relatively stable over the decades as shown in Figure 1. In our current study, there were no stillbirth cases of vasa previa or placenta previa. In summary, the most common aetiologies of stillbirths from the previous study by Fretts et al. from 1961 to 1988 were unexplained cases, intrauterine growth restriction and intra-partum asphyxia. In comparison, over the subsequent two decades, unexplained stillbirth was still found to be the most common cause, followed by the broad categories of “others” and abruptio placentae.

Figure 1.
Trends in the Etiology of Stillbirth 1960-2009
McGill University Health Centre
Royal Victoria Hospital, Montreal, Canada



DISCUSSION

Detailed stillbirth examinations have been performed at our institution for several decades allowing the evolution of the aetiologies of stillbirth to be evaluated in a cohort of over 150,000 births from this single centre over a 50-year period.

Recently, Cousens et al. estimated the global rate of stillbirths to be 2.64 million in 2009, compared to 3.03 million in 1995, a decline in the worldwide rate of 14.5%, from 22.1 to 18.9 per 1000 births between 1995 and 2009[2]. The majority of stillbirths occur in low-income countries and a WHO report in 2000 found that in underdeveloped countries, 60% of perinatal deaths are due to stillbirths compared to 40% in developed countries[14]. Under reporting is a major issue in developing countries given that half of stillbirths occur at home without appropriate prenatal care[15]. Cousens et al. emphasise the need for accurate data collection to gain a better understanding of the scope of the problem in order for global intervention programs to be planned[2].

A review by Fretts et al. evaluated strategies for stillbirth prevention in 113 articles[17]. Interventions including Rh immune prophylaxis and intra-partum monitoring have contributed to a decrease in the rates of stillbirth. Recognition of risk factors such as obesity, poor socioeconomic status and advanced maternal age will identify patients in whom appropriate management and surveillance during their pregnancies should be implemented in order to improve outcomes and prevent stillbirths[18, 19]. Although previously unexplained stillbirths have been noted to increase with advancing gestational age, the risk reportedly doubling after 40 weeks' gestation[20], our findings do not affirm this, with only 12% of all unexplained stillbirths

occurring beyond 40 weeks. This is likely due to increasing inductions of labour for post-dates pregnancy in our current practice, with few pregnancies going beyond 42 weeks. Improved outcomes for women with gestational diabetes are likely due to the intensive management and regular multidisciplinary follow-up provided at our institution[21].

In a retrospective analysis of nearly 30,000 term deliveries unexplained stillbirths represented 51% of cases[22] and in part this was attributable to incomplete assessments. In our data the rate of unexplained stillbirths is much lower at 26.7%. This is partially due to the routine approach of offering detailed fetal post-mortem examination or limited examination when a full autopsy is declined; even when fetal autopsy is declined the placenta is evaluated. Nonetheless, antepartum asphyxia of unknown origin remains the most common contributor to stillbirth (26.7%) with a significant proportion occurring in late pregnancy (40%). Perhaps more in-depth fetal surveillance with complimentary emphasis on placental function could help identify potential problems. Newer techniques including DNA analysis (e.g. array comparative genomic hybridization-CGH) and more comprehensive testing, e.g. cytogenetic analysis of placental tissue evaluating mosaicism, may shed light on some of these cases[23, 24]. Sebire et al. suggest using non-invasive imaging techniques, e.g. MRI for post-mortem examination of stillborn fetuses. The 99% acceptance rate by parents compared favourably to the 60% for conventional autopsy[25].

In conclusion, in our study, the total fetal death rate has decreased compared to previous studies at 3.2 per 1000 (an 73% reduction in five decades) with a complete autopsy available in 76% of cases. Unexplained antepartum asphyxia still remains the most frequent diagnosis for fetal

demise. Abruptio placentae, sepsis and intrauterine growth restriction are the next most common aetiologies of stillbirth. These improvements reflect a more standardised obstetrical care, better fetal surveillance and timely delivery of high-risk pregnancies as well as steps toward a more comprehensive evaluation of the stillbirth.

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Results: Amongst 79,410 births from 1989-2009, 217 stillbirths were included in our study. The mean maternal age was 31,05 (± 5.8) years. In 28.1% of cases, there was a prior history of subfertility. The mean gestational age at diagnosis was 32.69 (± 5.58) weeks, with a birth weight of 1,888 (± 1,084) grams. The main causes of stillbirth were unknown (26.7%), placental factors (19.8%) and abruptio placenta (12.9%). Other causes included hematogeneous or ascending infection (10.6%), fetal malformations (8.3%), maternal hypertension (3.2%), intrauterine growth restriction (2.8%), diabetes (1.8%) and intra-partum asphyxia (1.4%). Other fetal causes were found in 12.4% of cases.

Conclusions: Due to detailed pathological examination of most stillbirth cases over the last five decades at our tertiary obstetrical centre, we could study the trends in the etiology of stillbirths in a cohort of more than 150,000 births. In 50 years, the rate of stillbirth has decreased from 115 to 32 cases per 10,000 births from the 1960s to 2000s, which represents a reduction of 72%. Stillbirth from unknown cause remains the most common contributor, with 40% of these cases occurring in late pregnancy.

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. Despite the great numbers of papers recently published on stillbirths, we are one of the few institutions in North America who have been able to create a complete obstetrical and neonatal database with consistent pathological examination throughout the last five decades.

2. However, there are a few limitations to our paper. Given the fact that our institution is a tertiary referral centre, our specific patient populations, with a greater proportion of high-risk pregnancies, may not exactly represent the general patient population in most community hospitals. Our results may be somewhat influenced by this tertiary center bias.

3. Also, the study of individual aetiology is somehow limited to a small number of cases per decade given the decreasing incidence of stillbirths with improved obstetrical care in the past decades.

4. Another limitation is from the fact that 72 of our stillbirths could not be included in the analysis of the trend of aetiologies due to incomplete pathology examination or autopsy refusal. This represents almost a quarter of the cases of stillbirths during the study period. However, as protocols for stillbirth are being developed as standard obstetrical care, the use of autopsy examination should be more prevalent.

INTRODUCTION

Stillbirth is defined as the death before birth of a fetus ≥ 20th week of gestation or a weight ≥ 500g[1]. Worldwide, stillbirth remains the most prevalent adverse outcome of pregnancy, estimated at 2.64 million in 2009[2] and 1 in 160 pregnancies in the United States[3]. The rates of stillbirth remain highest in developing countries but likely underestimated due to the both poor access to obstetrical care and the limited recordkeeping[4]. Among the various recognized etiologies of stillbirth, obstetric complications and placental abnormalities remain the most common in developed countries[5]; however, a recent increase in the proportion of stillbirths caused by congenital malformations has been noted[6]. The rate of unknown cause has remained the same over the last decades[7-8]. Maternal obesity and advanced maternal age are now thought to contribute to an increasing proportion of stillbirths[9-10].

This study aims to examine and evaluate the rates and etiologies of stillbirths over the past 20 years at the McGill University Health Center (MUHC). A previous study at this institution evaluated the period from 1961-1988 and demonstrated that the major cause of death was unknown[11]. We will also compare our current data with the historical data previously derived.

MATERIAL AND METHODS

A retrospective cohort study was conducted at the McGill University Health Center (MUHC) with data from the Royal Victoria Hospital, a tertiary-care centre and one of the main referral centers in the province. At this institution it has for many decades been the standard practice for all patients with a stillbirth to be offered a complete fetal autopsy and for all placentas to routinely be examined by a specialised team of technicians and perinatal pathologists. Parents had to consent to the autopsy and placenta analysis. A detailed external and internal examination of the fetus with microscopic examination of fetal and placental tissues is performed following a standard protocol. Our pathology database was regularly updated with all available cases.

All autopsy reports of stillbirths delivered between 1989 and 2009 were retrieved from our pathology database. For this study, the definition of stillbirth was defined as the birth of a fetus weighing 500g or more with no signs of life. Pregnancy terminations were not included in this study..

We recognise that more than one cause may have contributed to any individual fetal death. To facilitate comparison with the earlier cohorts (1961-1988), with data collected similarly within our institution and published in 1992, the primary causes of fetal death were classified according to similar guidelines as described in Table 1[11]. Complete pathological examination with clinical correlation at departmental meeting was used to determine the most likely primary cause. The cases that were not attributable to any of the principal categories were classified as “others” with these in turn being sub-divided as fetal or placental causes, depending on the final autopsy conclusions. All specific causes, comprising the “others” category, are also listed in Table 1.

Table 1. Classification of primary causes of fetal death	
Abruptio placentae	Fetal death associated with antepartum bleeding and retroplacental blood clot, excluding placenta previa
Maternal diabetes	Otherwise unexplained fetal death of appropriate for gestational age infants of diabetic or glucose-intolerant mothers
Infection	Fetal death in which the fetus and/or the placenta show evidence of infection on pathologic examination, with or without clinical signs of maternal infection
Intrapartum asphyxia	Asphyxia related to labor and delivery, death without placental, cord, fetal, or maternal cause. This group is subdivided into deaths related to dystocia labor or malpresentation, and those otherwise unexplained deaths occurring during apparently normal labor.
Fetal growth restriction	Asphyxia or otherwise unexplained fetal death in a fetus 25% underweight (2.4^{th} percentile) for gestational age at time of death.
Isoimmunization	Abnormal maternal antibodies and evidence of excessive fetal erythropoiesis
Malformation	Potentially lethal anomalies take precedence over all other conditions
Maternal Hypertension	Otherwise unexplained fetal death of appropriate for gestational age infants in hypertensive mothers
Unknown cause	Death of an appropriate for gestational age fetus before labor with no evident fetal, maternal, or placental abnormality (with or without cord loops/knots)
Others – Placental causes	Includes placental insufficiency, placental infarct, cord accident, cord thrombosis, cord prolapse, vasculopathy
Others – Fetal causes	Includes fetal blood loss, hydrops, twin-to-twin transfusion syndrome, fetal-maternal hemorrhage, fetal shock, fetal coagulopathy, decreased uteroplacental blood flow

Medical charts of all pregnancy delivered at the MUHC, Montreal, Canada, are systematically reviewed by a specific team from our department. They retrieve all pertinent data from the charts to build the "Montreal Obstetrical and Neonatal Database" (MOND), which is a comprehensive computerised database of obstetrical and neonatal data for all deliveries at our centre. We used this database to retrieve relevant maternal information that could have affected pregnancy outcomes and be related to stillbirth. Accuracy of fetal characteristics including gestational age, birth weight and gender were also cross-referred between the pathology and the MOND database. Hypertension complicating pregnancy was defined as any hypertensive disorder

diagnosed during pregnancy, whether chronic (prior to 20 weeks of gestation), pregnancy-induced hypertension or pre-eclampsia. Diabetes at the time of delivery included impaired glucose tolerance and all classes of diabetes from A1 to T (White Classification)[12]. Subfertility was defined as at least one year of unprotected intercourse before the current pregnancy. Intrauterine growth restriction was defined as a birth weight less than the 5th percentile for gestational age following the United States National Reference for Fetal Growth[13]. Continuous variables were all described by mean values and standard deviations. Categorical variables were described by total numbers and percentages. Stillbirth rates were described per 10,000 live births as in the previous paper. Rates were used to compare data between two decades, and percentages were used when comparing data within the same decade. Descriptive analysis was conducted to present the results. The McGill University Health Centre's institutional review board granted scientific review and ethical approval for this study. Patient consent was obtained at the time of autopsy for diagnostic and research purposes.

RESULTS

From a cohort of 79,410 births that delivered at the Royal Victoria Hospital between 1989 and 2009, 332 pathology reports for stillborn fetuses were retrieved. Of those, 43 were identified as terminations of pregnancy for medical or fetal indications and were excluded. Of the remaining 289 stillbirths, 70 did not undergo complete autopsy examination, primarily due to parental refusal. The overall autopsy rate was therefore 76%. Two cases were rejected from the study because of possible interpretation bias. The first case was the death of a newborn, delivered at home and where death was declared at the hospital soon after birth. The second case was excluded because placental pathological examination had not been performed. The final study population consisted of 217 stillbirths, although overall rates for this period were calculated from the total 289 stillbirths.

Table 2. Baseline maternal and fetal characteristics of the 217 stillbirth cases

	Total cases N (%)	Mean (± SD)
Maternal age	--	31.05 ± 5.86
Gravida	--	2.48
Parity	--	0.80
Aborta	--	0.68
Multiple gestation	23 (10.6%)	--
Infertility	65 (30.0%)	--
Smoking	43 (19.8%)	--
Cannabis use	9 (4.2%)	--
Previous cesarean	21 (9.7%)	0.12
Cesarean birth	23 (10.6%)	--
Gestational hypertension	23 (10.6%)	--
Gestational diabetes	12 (5.5%)	--
Female fetuses	102 (47.0%)	--
Male fetuses	115 (53.0%)	--
Gestational age (weeks)	--	32.69 ± 5.58
Birth weight (gram)	--	1888 ± 1084

We first examined the maternal characteristics of these stillbirths (Table 2). The mean maternal age was 31.05 ± 5.86 years. The mean gravidity, parity and number of prior abortions were 2.48, 0.80 and 0.68 respectively. In our study population, 23 patients had a twin pregnancy; 43 were smokers; 23 had hypertension and 12 had diabetes. In 65 cases, there was a prior history of subfertility. The mean gestational age at the stillbirth delivery was 32.69 ± 5.58 weeks, with a birth weight of 1888 ± 1084 grams. Of the 217 cases of stillbirth with full autopsy, 142 cases occurred in the decade from 1989 to 1999, and 75 cases occurred between 2000-2009, which is approximately a 50% reduction in the number of stillbirths from one decade to the next (Table 3). There are 52 stillbirth cases that occurred before 28 weeks gestation; 72 cases between 28 and 34 weeks; 79 cases between 34 and 40 weeks; and the remaining 14 cases after 40 weeks (Table 3). Prematurity was proportionally similar (24% before 28 weeks and 57% before 34 weeks) for both studied decades. The rate of pregnancies exceeding 40 weeks also remained unchanged from 1989-1999 to 2000-2009.

TABLE 3. Fetal deaths by gestational age from 1989-2009

Gestational age (weeks)	Cases from 1989–1999 (%)	Cases from 2000–2009 (%)	TOTAL CASES (%)
< 28	34 (23.9)	18 (24.0)	52 (24.0)
28 - 34	47 (33.1)	25 (33.3)	72 (33.2)
34^{+1} - 40	51 (35.9)	28 (37.3)	79 (36.4)
> 40	10 (7.0)	4 (5.3)	14 (6.5)
TOTAL	**142 (65.4)**	**75 (34.6)**	**217**

The most common cause of stillbirth was unknown (n=58) (Table 4). Stillbirth from unknown cause has decreased from 45 cases between 1989 and 1999 to only 13 cases in the subsequent decade. This represents a near 50% reduction from the previous decade. We also evaluated the unexplained fetal deaths by gestational age (Table 5). Nearly 40% (n=23) of these cases occurred

in later pregnancy, between 34 and 40 weeks. There were only seven cases in the post-dates period, 12 cases in gestations < 28 weeks and 16 cases in gestations between 28 and 34 weeks.

TABLE 4. Causes of death among stillbirths from 1989-2009

CAUSE	Cases from 1989–1999 (%)	Cases from 2000–2009 (%)	TOTAL CASES (%)
Abruptio placenta	15 (10.6)	13 (17.3)	28 (12.9)
Maternal diabetes	4 (2.8)	0	4 (1.8)
Infection	19 (13.4)	4 (5.3)	23 (10.6)
Chorioamnionitis	*14 (9.9)*	*3 (4.0)*	
Cytomegalovirus	*0*	*1 (1.3)*	
Parvorirus B19	*3 (2.1)*	*0*	
Villitis	*2 (1.4)*	*0*	
Intrapartum asphyxia	2 (1.4)	1 (1.3)	3 (1.4)
Intrauterine growth restriction	6 (4.2)	0	6 (2.8)
Malformation	12 (8.4)	6 (8.0)	18 (8.3)
Maternal Hypertension	5 (3.5)	2 (2.6)	7 (3.2)
Unknown cause	45 (31.7)	13 (17.3)	58 (26.7)
Other – placental causes	18 (12.7)	25 (33.3)	43 (19.8)
Other – fetal causes	16 (11.7)	11 (14.7)	27 (12.4)
TOTAL	**142 (65.4)**	**75 (34.6)**	**217**

TABLE 5. Unexplained fetal deaths by gestational age from 1989-2009

Gestational age (weeks)	Cases from 1989–1999 (%)	Cases from 2000–2009 (%)	TOTAL CASES (%)
< 28	7 (15.5)	5 (38.4)	12 (20.7)
28 - 34	12 (26.7)	4 (30.8)	16 (27.6)
34^{+1} - 40	19 (42.2)	4 (30.8)	23 (39.6)
> 40	7 (15.5)	0	7 (12.1)
TOTAL	**45**	**13**	**58**

Abruptio placentae was the second most common cause, identified in 28 cases overall with a similar number of cases in both decades (15 and 13 cases respectively). Although this appears to represent a slight increase in the cases of stillbirth secondary to abruptio placenta from 10.6% to

17.3%, the rates remained similar (3.6 versus 3.5 cases per 10,000 births respectively) and the difference was not statistically significant (p=0.116). Infection, including ascending and hematogeneous infections, was the primary factor in 23 cases with a marked decrease of cases in 2000-2009 compared to 1989-1999 (1.1 versus 4.5 cases per 10,000 births respectively), a difference that reached significance (p=0.05). Most infectious cases were from ascending chorioamnionitis with 14 cases occurring during 1989-1999 and only three cases during 2000-2009; the former decade including three cases of Parvovirus B19 and two of unspecified villitis and the latter including one case of Cytomegalovirus. Intrauterine growth restriction was identified as the primary etiological factor in six stillbirths, none of which occurred in the later decade. Given the small number of cases this difference was not found to be statistically significant (p=0.076).

Other placental or umbilical cord factors accounted for 43 cases; which represents an increase of 4.3 to 6.7 cases per 10,000 births from 1989-1999 to 2000-2009. The majority of these were placental infarcts and cord accidents: 15 cases and 16 cases, respectively. The other cases include placental insufficiency, cord prolapse, thrombosis and vasculopathy (Table 6). Fetal malformations accounted for 18 cases whilst other fetal causes, such as fetal blood loss, twin-to-twin transfusion syndrome, hydrops, feto-maternal haemorrhage, fetal shock and coagulopathy, accounted for 27 cases. Although the overall rate for a fetal cause of the stillbirth remained stable, there were no cases of hydrops in the latter decade 2000-2009. The remaining cases were attributable to maternal hypertensive disorders (3.2%), diabetes (1.8%) or intra-partum asphyxia (1.4%); the frequencies of these were essentially unchanged across the two decades except for

diabetes which was not a primary factor in any cases in the period 2000-9 (Table 4). Of note, no stillbirth consequent to iso-immunization occurred during either of these two decades.

Table 6. Fetal deaths due to miscellaneous causes

	Cases from 1989-1999 (%)	Cases from 2000-2009 (%)	TOTAL CASES (%)
PLACENTAL CAUSES	**18 (41.9)**	**25 (58.1)**	**43**
Placental insufficiency	0	5 (20.0)	5 (11.6)
Placental infarct	7 (38.9)	8 (32.0)	15 (34.9)
Cord accident	9 (50.0)	7 (28.0)	16 (37.2)
Cord prolapse	0	1 (4.0)	1 (2.3)
Cord thrombosis	0	2 (8.0)	2 (4.7)
Vasculopathy	2 (11.1)	2 (8.0)	4 (9.3)
FETAL CAUSES	**16 (59.2)**	**11 (40.7)**	**27**
Fetal blood loss	2 (12.5)	2 (18.2)	4 (14.8)
Twin-to-twin transfusion	4 (25.0	2 (18.2)	6 (22.2)
Hydrops	5 (31.2)	0	5 (18.5)
Fetal-maternal hemorrhage	4 (25.0)	3 (27.3)	7 (25.9)
Fetal shock	1 (6.3)	1 (9.1)	2 (7.4)
Fetal coagulopathy	0	2 (18.2)	2 (7.4)
Decreased uteroplacental blood flow	0	1 (9.1)	1 (3.7)

Our study results were compared with data from previous decades at this single institution. First of all, the total number of births per decade has increased significantly from 29,101 births in the 1960s to 37,537 births in the 2000s. There was a major overall improvement in the rates of stillbirths over the decades: 115/10,000 births in the 1960s, 51/10,000 births in the 1980s, 41/10,000 births in the 1990s and 32/10,000 births in the 2000s. The above rates took into account the 72 stillbirth cases excluded from the study due to incomplete pathological

examination. This represents a 72% reduction in the overall rate of stillbirths from 1960-1969 to 2000-2009. Specific etiologies of the 217 examined stillbirths were also compared to the previous study at the same institution. Unexplained stillbirths decreased from 38.1/10,000 births in the 1960s to 20.6/10,000 in the 1970s, 13.6/10,000 in the 1980s and 7.3/10,000 in our current study. The numbers of stillbirths secondary to abruptio placentae was relatively stable in our study period: 3.6/10,000 births in the 1990s and 3.5/10,000 births in the 2000s. This was a significant reduction from previous decades: 11.6/10,000 in 1960s, 11.2/10,000 in 1970s and 7.2/10,000 in the 1980s. The rate of stillbirths due to infectious causes remained stable at 4.5/10,000 births over the decades until the most recent decades (2000s) where the rate dropped to 1.1/10,000 births. The rates of stillbirths from intra-partum asphyxia, malformations, diabetes and maternal hypertension have dramatically decreased over the decades (Figure 1). There are no cases of Rhesus iso-immunization compared to 4.3/10,000 births in the 1960s. It would be difficult to compare the rates of stillbirths from other causes, as these were not classified as placental or fetal causes in the previous study. However this category remained relatively stable over the decades as shown in Figure 1. In our current study, there were no stillbirth cases of vasa previa or placenta previa. In summary, the most common etiologies of stillbirths from the previous study by Fretts et al. from 1961 to 1988 were unexplained cases, intrauterine growth restriction and intra-partum asphyxia. In comparison, over the subsequent two decades, unexplained stillbirth was still found to be the most common cause, followed by the broad categories of “others” and abruptio placentae.

DISCUSSION

Detailed stillbirth examinations have been performed at our institution for several decades allowing the evolution of the aetiologies of stillbirth to be evaluated in a cohort of over 150,000 births from this single centre over a 50-year period.

Recently, Cousens et al. estimated the global rate of stillbirths to be 2.64 million in 2009, compared to 3.03 million in 1995, a decline in the worldwide rate of 14.5%, from 22.1 to 18.9 per 1000 births between 1995 and 2009[2]. The majority of stillbirths occur in low-income countries and a WHO report in 2000 found that in developing countries, 60% of perinatal deaths are due to stillbirths compared to 40% in developed countries[14]. Under reporting is a major issue in developing countries given that half of stillbirths occur at home without appropriate prenatal care[15]. Cousens et al. emphasise the need for accurate data collection to gain a better understanding of the scope of the problem in order for global intervention programs to be planned[2].

A review by Fretts et al. evaluated strategies for stillbirth prevention in 113 articles[16]. Interventions including Rh immune prophylaxis and intra-partum monitoring have contributed to a decrease in the rates of stillbirth. Recognition of risk factors such as obesity, poor socioeconomic status and advanced maternal age will identify patients in whom appropriate management and surveillance during their pregnancies should be implemented in order to improve outcomes and prevent stillbirths[17, 18]. Although previously unexplained stillbirths have been noted to increase with advancing gestational age, the risk reportedly doubling after 40

weeks' gestation[19], our findings do not affirm this, with only 12% of all unexplained stillbirths occurring beyond 40 weeks. This is likely due to increasing inductions of labour for post-dates pregnancy in our current practice, with few pregnancies going beyond 42 weeks. Improved outcomes for women with gestational diabetes are likely due to the intensive management and regular multidisciplinary follow-up provided at our institution[20].

In a retrospective analysis of nearly 30,000 term deliveries unexplained stillbirths represented 51% of stillbirths[21] and in part this was attributable to incomplete assessments. In our data the rate of unexplained stillbirths is much lower at 26.7%. This is partially due to the routine approach of offering detailed fetal post-mortem examination or limited examination when a full autopsy is declined; even when fetal autopsy is declined the placenta is evaluated. Nonetheless, asphyxia of unknown origin remains the most common contributor to stillbirth (26.7%) with a significant proportion occurring in late pregnancy (40%). Perhaps more in-depth fetal surveillance with complimentary emphasis on placental function could help identify potential problems. Newer techniques including DNA analysis (e.g. array comparative genomic hybridization-CGH) and more comprehensive testing, e.g. cytogenetic analysis of placental tissue evaluating mosaicism, may shed light on some of these cases[22, 23]. Sebire et al. suggest using non-invasive imaging techniques from multiple European studies between 1995 and 2010, e.g. MRI for post-mortem examination of stillborn fetuses. The 99% acceptance rate by parents compared favourably to the 60% for conventional autopsy[24].

In conclusion, in our study, the total fetal death rate has decreased compared to previous studies at 3.2 per 1000 (a 72% reduction in five decades from 1960-1969 to 2000-2009) with a complete

autopsy available in 76% of cases. Stillbirth from unknown cause still remains the most frequent diagnosis for fetal demise. Abruptio placentae, sepsis and intrauterine growth restriction are the next most common aetiologies of stillbirth. These improvements reflect a more standardised obstetrical care, better fetal surveillance and timely delivery of high-risk pregnancies as well as steps toward a more comprehensive evaluation of the stillbirth.

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Contribution to Authorship:

Dr. Karen Wou was the main author involved in the project. She worked on the acquisition, analysis and interpretation of data, and she was involved in the final manuscript preparation.

Dr. Marie-Pier Ouellet performed the review of literature, acquisition and analysis of data, and preparation of the final manuscript.

Dr. Brown was involved in the initial study design, the data analysis, the manuscript revision and approval for publication. He also supervised Dr. Wou and M. Ouellet at all stages of the project.

Dr. Chen was involved in the initial study design, the data collection and interpretation, the review and analysis of all the pathology reports included in the study. She was also involved in the manuscript revision and approval for publication and supervised each step of the project.

Competing interests: There are no competing interests

Data Sharing Statement: No additional data are available.

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Comparison of the etiology of stillbirth over five decades in a single centre: a retrospective study

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Funding: None

Competing interests: None

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ABSTRACT

Comparison of the etiology of stillbirth over five decades in a single centre: a retrospective study

Objective: To compare the rates and etiologies of stillbirth over the past 50 years.

Study Design: We reviewed all autopsy reports for stillbirths occurring between 1989 and 2009 at the McGill University Health Centre to determine the pathological etiology of stillbirths. We also reviewed maternal characteristics. We compared our results with a previous study published in 1992 on etiologies of stillbirth from 1961-1988 at the same institution.

Results: Amongst 79,410 births from 1989-2009, 217 stillbirths were included in our study. The mean maternal age was 31,05 (± 5.8) years. In 28.1% of cases, there was a prior history of subfertility. The mean gestational age at diagnosis was 32.69 (± 5.58) weeks, with a birth weight of 1,888 (± 1,084) grams. The main causes of stillbirth were unknown (26.7%), placental factors (19.8%) and abruptio placenta (12.9%). Other causes included hematogeneous or ascending infection (10.6%), fetal malformations (8.3%), maternal hypertension (3.2%), intrauterine growth restriction (2.8%), diabetes (1.8%) and intra-partum asphyxia (1.4%). Other fetal causes were found in 12.4% of cases.

Conclusions: Due to detailed pathological examination of most stillbirth cases over the last five decades at our tertiary obstetrical centre, we could study the trends in the etiology of stillbirths in a cohort of more than 150,000 births. In 50 years, the rate of stillbirth has decreased from 115 to 32 cases per 10,000 births from the 1960s to 2000s, which represents a reduction of 72%. Stillbirth from unknown cause remains the most common contributor, with 40% of these cases occurring in late pregnancy.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

1. Despite the great numbers of papers recently published on stillbirths, we are one of the few institutions in North America who have been able to create a complete obstetrical and neonatal database with consistent pathological examination throughout the last five decades.

2. However, there are a few limitations to our paper. Given the fact that our institution is a tertiary referral centre, our specific patient populations, with a greater proportion of high-risk pregnancies, may not exactly represent the general patient population in most community hospitals. Our results may be somewhat influenced by this tertiary center bias.

3. Also, the study of individual aetiology is somehow limited to a small number of cases per decade given the decreasing incidence of stillbirths with improved obstetrical care in the past decades.

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INTRODUCTION

Stillbirth is defined as the death before birth of a fetus ≥ 20th week of gestation or a weight ≥ 500g[1]. Worldwide, stillbirth remains the most prevalent adverse outcome of pregnancy, estimated at 2.64 million in 2009[2] and 1 in 160 pregnancies in the United States[3]. The rates of stillbirth remain highest in developing countries but likely underestimated due to the both poor access to obstetrical care and the limited recordkeeping[4]. Among the various recognized etiologies of stillbirth, obstetric complications and placental abnormalities remain the most common in developed countries[5]; however, a recent increase in the proportion of stillbirths caused by congenital malformations has been noted[6]. The rate of unknown cause has remained the same over the last decades[7-8]. Maternal obesity and advanced maternal age are now thought to contribute to an increasing proportion of stillbirths[9-10].

This study aims to examine and evaluate the rates and etiologies of stillbirths over the past 20 years at the McGill University Health Center (MUHC). A previous study at this institution evaluated the period from 1961-1988 and demonstrated that the major cause of death was unknown[11]. We will also compare our current data with the historical data previously derived.

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MATERIAL AND METHODS

A retrospective cohort study was conducted at the McGill University Health Center (MUHC) with data from the Royal Victoria Hospital, a tertiary-care centre and one of the main referral centers in the province. At this institution it has for many decades been the standard practice for all patients with a stillbirth to be offered a complete fetal autopsy and for all placentas to routinely be examined by a specialised team of technicians and perinatal pathologists. Parents had to consent to the autopsy and placenta analysis. A detailed external and internal examination of the fetus with microscopic examination of fetal and placental tissues is performed following a standard protocol. Our pathology database was regularly updated with all available cases.

All autopsy reports of stillbirths delivered between 1989 and 2009 were retrieved from our pathology database. For this study, the definition of stillbirth was defined as the birth of a fetus weighing 500g or more with no signs of life. Pregnancy terminations were not included in this study..

We recognise that more than one cause may have contributed to any individual fetal death. To facilitate comparison with the earlier cohorts (1961-1988), with data collected similarly within our institution and published in 1992, the primary causes of fetal death were classified according to similar guidelines as described in Table 1[11]. Complete pathological examination with clinical correlation at departmental meeting was used to determine the most likely primary cause. The cases that were not attributable to any of the principal categories were classified as "others" with these in turn being sub-divided as fetal or placental causes, depending on the final autopsy conclusions. All specific causes, comprising the "others" category, are also listed in Table 1.

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Table 1. Classification of primary causes of fetal death	
Abruptio placentae	Fetal death associated with antepartum bleeding and retroplacental blood clot, excluding placenta previa
Maternal diabetes	Otherwise unexplained fetal death of appropriate for gestational age infants of diabetic or glucose-intolerant mothers
Infection	Fetal death in which the fetus and/or the placenta show evidence of infection on pathologic examination, with or without clinical signs of maternal infection
Intrapartum asphyxia	Asphyxia related to labor and delivery, death without placental, cord, fetal, or maternal cause. This group is subdivided into deaths related to dystocia labor or malpresentation, and those otherwise unexplained deaths occurring during apparently normal labor.
Fetal growth restriction	Asphyxia or otherwise unexplained fetal death in a fetus 25% underweight (2.4^{th} percentile) for gestational age at time of death.
Isoimmunization	Abnormal maternal antibodies and evidence of excessive fetal erythropoiesis
Malformation	Potentially lethal anomalies take precedence over all other conditions
Maternal Hypertension	Otherwise unexplained fetal death of appropriate for gestational age infants in hypertensive mothers
Unknown cause	Death of an appropriate for gestational age fetus before labor with no evident fetal, maternal, or placental abnormality (with or without cord loops/knots)
Others – Placental causes	Includes placental insufficiency, placental infarct, cord accident, cord thrombosis, cord prolapse, vasculopathy
Others – Fetal causes	Includes fetal blood loss, hydrops, twin-to-twin transfusion syndrome, fetal-maternal hemorrhage, fetal shock, fetal coagulopathy, decreased uteroplacental blood flow

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Medical charts of all pregnancy delivered at the MUHC, Montreal, Canada, are systematically reviewed by a specific team from our department. They retrieve all pertinent data from the charts to build the "Montreal Obstetrical and Neonatal Database" (MOND), which is a comprehensive computerised database of obstetrical and neonatal data for all deliveries at our centre. We used this database to retrieve relevant maternal information that could have affected pregnancy outcomes and be related to stillbirth. Accuracy of fetal characteristics including gestational age, birth weight and gender were also cross-referred between the pathology and the MOND database. Hypertension complicating pregnancy was defined as any hypertensive disorder

diagnosed during pregnancy, whether chronic (prior to 20 weeks of gestation), pregnancy-induced hypertension or pre-eclampsia. Diabetes at the time of delivery included impaired glucose tolerance and all classes of diabetes from A1 to T (White Classification)[12]. Subfertility was defined as at least one year of unprotected intercourse before the current pregnancy. Intrauterine growth restriction was defined as a birth weight less than the 5th percentile for gestational age following the United States National Reference for Fetal Growth[13]. Continuous variables were all described by mean values and standard deviations. Categorical variables were described by total numbers and percentages. Stillbirth rates were described per 10,000 live births as in the previous paper. Rates were used to compare data between two decades, and percentages were used when comparing data within the same decade. Descriptive analysis was conducted to present the results. The McGill University Health Centre's institutional review board granted scientific review and ethical approval for this study. Patient consent was obtained at the time of autopsy for diagnostic and research purposes.

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RESULTS

From a cohort of 79,410 births that delivered at the Royal Victoria Hospital between 1989 and 2009, 332 pathology reports for stillborn fetuses were retrieved. Of those, 43 were identified as terminations of pregnancy for medical or fetal indications and were excluded. Of the remaining 289 stillbirths, 70 did not undergo complete autopsy examination, primarily due to parental refusal. The overall autopsy rate was therefore 76%. Two cases were rejected from the study because of possible interpretation bias. The first case was the death of a newborn, delivered at home and where death was declared at the hospital soon after birth. The second case was excluded because placental pathological examination had not been performed. The final study population consisted of 217 stillbirths, although overall rates for this period were calculated from the total 289 stillbirths.

Table 2. Baseline maternal and fetal characteristics of the 217 stillbirth cases

	Total cases N (%)	Mean (± SD)
Maternal age	--	31.05 ± 5.86
Gravida	--	2.48
Parity	--	0.80
Aborta	--	0.68
Multiple gestation	23 (10.6%)	--
Infertility	65 (30.0%)	--
Smoking	43 (19.8%)	--
Cannabis use	9 (4.2%)	--
Previous cesarean	21 (9.7%)	0.12
Cesarean birth	23 (10.6%)	--
Gestational hypertension	23 (10.6%)	--
Gestational diabetes	12 (5.5%)	--
Female fetuses	102 (47.0%)	--
Male fetuses	115 (53.0%)	--
Gestational age (weeks)	--	32.69 ± 5.58
Birth weight (gram)	--	1888 ± 1084

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We first examined the maternal characteristics of these stillbirths (Table 2). The mean maternal age was 31.05 ± 5.86 years. The mean gravidity, parity and number of prior abortions were 2.48, 0.80 and 0.68 respectively. In our study population, 23 patients had a twin pregnancy; 43 were smokers; 23 had hypertension and 12 had diabetes. In 65 cases, there was a prior history of subfertility. The mean gestational age at the stillbirth delivery was 32.69 ± 5.58 weeks, with a birth weight of 1888 ± 1084 grams. Of the 217 cases of stillbirth with full autopsy, 142 cases occurred in the decade from 1989 to 1999, and 75 cases occurred between 2000-2009, which is approximately a 50% reduction in the number of stillbirths from one decade to the next (Table 3). There are 52 stillbirth cases that occurred before 28 weeks gestation; 72 cases between 28 and 34 weeks; 79 cases between 34 and 40 weeks; and the remaining 14 cases after 40 weeks (Table 3). Prematurity was proportionally similar (24% before 28 weeks and 57% before 34 weeks) for both studied decades. The rate of pregnancies exceeding 40 weeks also remained unchanged from 1989-1999 to 2000-2009.

TABLE 3. Fetal deaths by gestational age from 1989-2009

Gestational age (weeks)	Cases from 1989–1999 (%)	Cases from 2000–2009 (%)	TOTAL CASES (%)
< 28	34 (23.9)	18 (24.0)	52 (24.0)
28 - 34	47 (33.1)	25 (33.3)	72 (33.2)
34^{+1} - 40	51 (35.9)	28 (37.3)	79 (36.4)
> 40	10 (7.0)	4 (5.3)	14 (6.5)
TOTAL	**142 (65.4)**	**75 (34.6)**	**217**

The most common cause of stillbirth was unknown (n=58) (Table 4). Stillbirth from unknown cause has decreased from 45 cases between 1989 and 1999 to only 13 cases in the subsequent decade. This represents a near 50% reduction from the previous decade. We also evaluated the unexplained fetal deaths by gestational age (Table 5). Nearly 40% (n=23) of these cases occurred

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in later pregnancy, between 34 and 40 weeks. There were only seven cases in the post-dates period, 12 cases in gestations < 28 weeks and 16 cases in gestations between 28 and 34 weeks.

TABLE 4. Causes of death among stillbirths from 1989-2009

CAUSE	Cases from 1989–1999 (%)	Cases from 2000–2009 (%)	TOTAL CASES (%)
Abruptio placenta	15 (10.6)	13 (17.3)	28 (12.9)
Maternal diabetes	4 (2.8)	0	4 (1.8)
Infection	19 (13.4)	4 (5.3)	23 (10.6)
Chorioamnionitis	*14 (9.9)*	*3 (4.0)*	
Cytomegalovirus	*0*	*1 (1.3)*	
Parvorirus B19	*3 (2.1)*	*0*	
Villitis	*2 (1.4)*	*0*	
Intrapartum asphyxia	2 (1.4)	1 (1.3)	3 (1.4)
Intrauterine growth restriction	6 (4.2)	0	6 (2.8)
Malformation	12 (8.4)	6 (8.0)	18 (8.3)
Maternal Hypertension	5 (3.5)	2 (2.6)	7 (3.2)
Unknown cause	45 (31.7)	13 (17.3)	58 (26.7)
Other – placental causes	18 (12.7)	25 (33.3)	43 (19.8)
Other – fetal causes	16 (11.7)	11 (14.7)	27 (12.4)
TOTAL	**142 (65.4)**	**75 (34.6)**	**217**

TABLE 5. Unexplained fetal deaths by gestational age from 1989-2009

Gestational age (weeks)	Cases from 1989–1999 (%)	Cases from 2000–2009 (%)	TOTAL CASES (%)
< 28	7 (15.5)	5 (38.4)	12 (20.7)
28 - 34	12 (26.7)	4 (30.8)	16 (27.6)
34^{+1} - 40	19 (42.2)	4 (30.8)	23 (39.6)
> 40	7 (15.5)	0	7 (12.1)
TOTAL	**45**	**13**	**58**

Abruptio placentae was the second most common cause, identified in 28 cases overall with a similar number of cases in both decades (15 and 13 cases respectively). Although this appears to represent a slight increase in the cases of stillbirth secondary to abruptio placenta from 10.6% to

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17.3%, the rates remained similar (3.6 versus 3.5 cases per 10,000 births respectively) and the difference was not statistically significant (p=0.116). Infection, including ascending and hematogeneous infections, was the primary factor in 23 cases with a marked decrease of cases in 2000-2009 compared to 1989-1999 (1.1 versus 4.5 cases per 10,000 births respectively), a difference that reached significance (p=0.05). Most infectious cases were from ascending chorioamnionitis with 14 cases occurring during 1989-1999 and only three cases during 2000-2009; the former decade including three cases of Parvovirus B19 and two of unspecified villitis and the latter including one case of Cytomegalovirus. Intrauterine growth restriction was identified as the primary etiological factor in six stillbirths, none of which occurred in the later decade. Given the small number of cases this difference was not found to be statistically significant (p=0.076).

Other placental or umbilical cord factors accounted for 43 cases; which represents an increase of 4.3 to 6.7 cases per 10,000 births from 1989-1999 to 2000-2009. The majority of these were placental infarcts and cord accidents: 15 cases and 16 cases, respectively. The other cases include placental insufficiency, cord prolapse, thrombosis and vasculopathy (Table 6). Fetal malformations accounted for 18 cases whilst other fetal causes, such as fetal blood loss, twin-to-twin transfusion syndrome, hydrops, feto-maternal haemorrhage, fetal shock and coagulopathy, accounted for 27 cases. Although the overall rate for a fetal cause of the stillbirth remained stable, there were no cases of hydrops in the latter decade 2000-2009. The remaining cases were attributable to maternal hypertensive disorders (3.2%), diabetes (1.8%) or intra-partum asphyxia (1.4%); the frequencies of these were essentially unchanged across the two decades except for

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diabetes which was not a primary factor in any cases in the period 2000-9 (Table 4). Of note, no stillbirth consequent to iso-immunization occurred during either of these two decades.

Table 6. Fetal deaths due to miscellaneous causes

	Cases from 1989-1999 (%)	Cases from 2000-2009 (%)	TOTAL CASES (%)
PLACENTAL CAUSES	**18 (41.9)**	**25 (58.1)**	**43**
Placental insufficiency	0	5 (20.0)	5 (11.6)
Placental infarct	7 (38.9)	8 (32.0)	15 (34.9)
Cord accident	9 (50.0)	7 (28.0)	16 (37.2)
Cord prolapse	0	1 (4.0)	1 (2.3)
Cord thrombosis	0	2 (8.0)	2 (4.7)
Vasculopathy	2 (11.1)	2 (8.0)	4 (9.3)
FETAL CAUSES	**16 (59.2)**	**11 (40.7)**	**27**
Fetal blood loss	2 (12.5)	2 (18.2)	4 (14.8)
Twin-to-twin transfusion	4 (25.0	2 (18.2)	6 (22.2)
Hydrops	5 (31.2)	0	5 (18.5)
Fetal-maternal hemorrhage	4 (25.0)	3 (27.3)	7 (25.9)
Fetal shock	1 (6.3)	1 (9.1)	2 (7.4)
Fetal coagulopathy	0	2 (18.2)	2 (7.4)
Decreased uteroplacental blood flow	0	1 (9.1)	1 (3.7)

Our study results were compared with data from previous decades at this single institution. First of all, the total number of births per decade has increased significantly from 29,101 births in the 1960s to 37,537 births in the 2000s. There was a major overall improvement in the rates of stillbirths over the decades: 115/10,000 births in the 1960s, 51/10,000 births in the 1980s, 41/10,000 births in the 1990s and 32/10,000 births in the 2000s. The above rates took into account the 72 stillbirth cases excluded from the study due to incomplete pathological examination. This represents a 72% reduction in the overall rate of stillbirths from 1960-1969 to

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2000-2009. Specific etiologies of the 217 examined stillbirths were also compared to the previous study at the same institution. Unexplained stillbirths decreased from 38.1/10,000 births in the 1960s to 20.6/10,000 in the 1970s, 13.6/10,000 in the 1980s and 7.3/10,000 in our current study. The numbers of stillbirths secondary to abruptio placentae was relatively stable in our study period: 3.6/10,000 births in the 1990s and 3.5/10,000 births in the 2000s. This was a significant reduction from previous decades: 11.6/10,000 in 1960s, 11.2/10,000 in 1970s and 7.2/10,000 in the 1980s. The rate of stillbirths due to infectious causes remained stable at 4.5/10,000 births over the decades until the most recent decades (2000s) where the rate dropped to 1.1/10,000 births. The rates of stillbirths from intra-partum asphyxia, malformations, diabetes and maternal hypertension have dramatically decreased over the decades (Figure 1). There are no cases of Rhesus iso-immunization compared to 4.3/10,000 births in the 1960s. It would be difficult to compare the rates of stillbirths from other causes, as these were not classified as placental or fetal causes in the previous study. However this category remained relatively stable over the decades as shown in Figure 1. In our current study, there were no stillbirth cases of vasa previa or placenta previa. In summary, the most common etiologies of stillbirths from the previous study by Fretts et al. from 1961 to 1988 were unexplained cases, intrauterine growth restriction and intra-partum asphyxia. In comparison, over the subsequent two decades, unexplained stillbirth was still found to be the most common cause, followed by the broad categories of "others" and abruptio placentae.

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Figure 1.
Trends in the Etiology of Stillbirth 1960-2009
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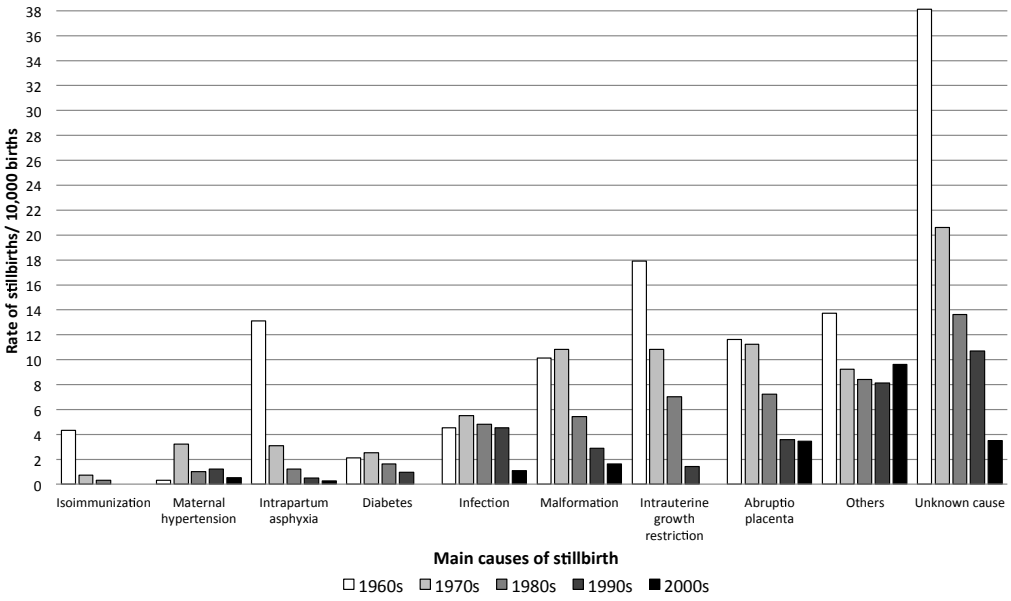

DISCUSSION

Detailed stillbirth examinations have been performed at our institution for several decades allowing the evolution of the aetiologies of stillbirth to be evaluated in a cohort of over 150,000 births from this single centre over a 50-year period.

Recently, Cousens et al. estimated the global rate of stillbirths to be 2.64 million in 2009, compared to 3.03 million in 1995, a decline in the worldwide rate of 14.5%, from 22.1 to 18.9 per 1000 births between 1995 and 2009[2]. The majority of stillbirths occur in low-income countries and a WHO report in 2000 found that in developing countries, 60% of perinatal deaths are due to stillbirths compared to 40% in developed countries[14]. Under reporting is a major issue in developing countries given that half of stillbirths occur at home without appropriate prenatal care[15]. Cousens et al. emphasise the need for accurate data collection to gain a better understanding of the scope of the problem in order for global intervention programs to be planned[2].

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A review by Fretts et al. evaluated strategies for stillbirth prevention in 113 articles[16]. Interventions including Rh immune prophylaxis and intra-partum monitoring have contributed to a decrease in the rates of stillbirth. Recognition of risk factors such as obesity, poor socioeconomic status and advanced maternal age will identify patients in whom appropriate management and surveillance during their pregnancies should be implemented in order to improve outcomes and prevent stillbirths[17, 18]. Although previously unexplained stillbirths have been noted to increase with advancing gestational age, the risk reportedly doubling after 40 weeks' gestation[19], our findings do not affirm this, with only 12% of all unexplained stillbirths

occurring beyond 40 weeks. This is likely due to increasing inductions of labour for post-dates pregnancy in our current practice, with few pregnancies going beyond 42 weeks. Improved outcomes for women with gestational diabetes are likely due to the intensive management and regular multidisciplinary follow-up provided at our institution[20].

In a retrospective analysis of nearly 30,000 term deliveries unexplained stillbirths represented 51% of stillbirths[21] and in part this was attributable to incomplete assessments. In our data the rate of unexplained stillbirths is much lower at 26.7%. This is partially due to the routine approach of offering detailed fetal post-mortem examination or limited examination when a full autopsy is declined; even when fetal autopsy is declined the placenta is evaluated. Nonetheless, asphyxia of unknown origin remains the most common contributor to stillbirth (26.7%) with a significant proportion occurring in late pregnancy (40%). Perhaps more in-depth fetal surveillance with complimentary emphasis on placental function could help identify potential problems. Newer techniques including DNA analysis (e.g. array comparative genomic hybridization-CGH) and more comprehensive testing, e.g. cytogenetic analysis of placental tissue evaluating mosaicism, may shed light on some of these cases[22, 23]. Sebire et al. suggest using non-invasive imaging techniques from multiple European studies between 1995 and 2010, e.g. MRI for post-mortem examination of stillborn fetuses. The 99% acceptance rate by parents compared favourably to the 60% for conventional autopsy[24].

In conclusion, in our study, the total fetal death rate has decreased compared to previous studies at 3.2 per 1000 (a~~n~~ 72% reduction in five decades from 1960-1969 to 2000-2009) with a complete autopsy available in 76% of cases. Stillbirth from unknown cause still remains the most

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frequent diagnosis for fetal demise. Abruptio placentae, sepsis and intrauterine growth restriction are the next most common aetiologies of stillbirth. These improvements reflect a more standardised obstetrical care, better fetal surveillance and timely delivery of high-risk pregnancies as well as steps toward a more comprehensive evaluation of the stillbirth.

Acknowledgements: None

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Figure 1.
Trends in the Etiology of Stillbirth 1960-2009
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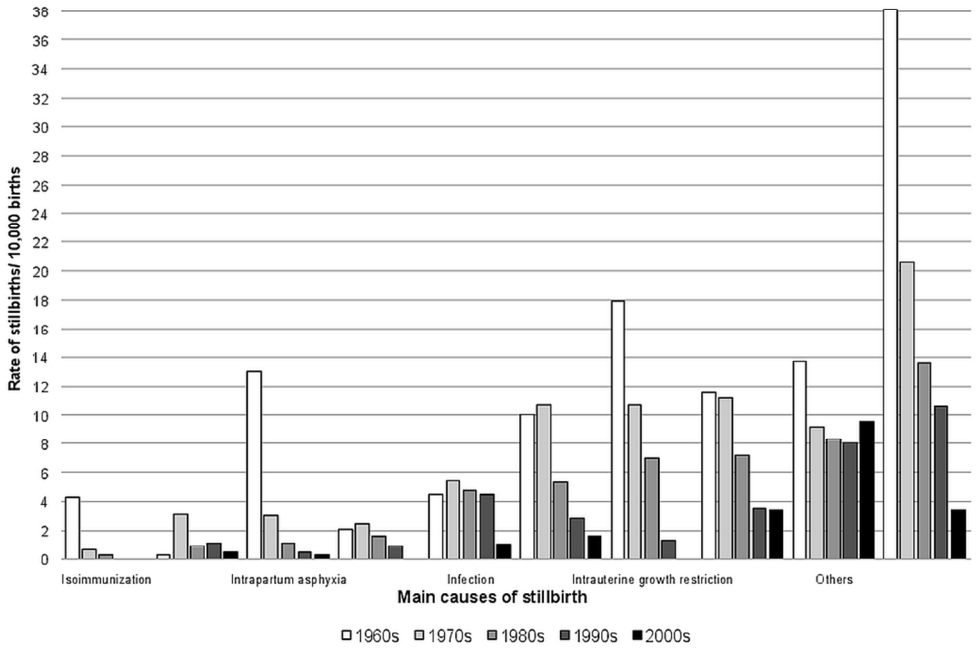

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